Graphene coatings for chemotherapy: avoiding silver-mediated degradation

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Graphene coatings for chemotherapy; Avoiding silver-mediated degradation

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Abstract

Chemotherapy treatment usually involves the delivery of fluorouracil (5-Fu) together with other drugs through central venous catheters. Catheters and their connectors are increasingly treated with silver or argentic alloys/compounds. Complications arising from broken catheters are common, leading to additional suffering for patients and increased medical costs. Here, we uncover a likely cause of such failure through a study of the surface chemistry relevant to chemotherapy drug delivery, i.e. between 5-Fu and silver. We show that silver catalytically decomposes 5-Fu, compromising the efficacy of the chemotherapy treatment. Furthermore, HF is released as a product, which will be damaging to both patient and catheter. We demonstrate that graphene surfaces inhibit this undesirable reaction and would offer superior performance as nanoscale coatings in cancer treatment applications.

5-Fluorouracil (5-Fu) is one of the most commonly used drugs in chemotherapy treatments [1–4]. 5-Fu works by inhibiting thymidine, a nucleoside required for DNA replication and necessary for cancer cells to reproduce [3]. The administration of 5-Fu into the human body is generally accomplished via a central venous catheter. Catheters are made of polymeric materials such as polyurethane and silicone [5] and they are prone to degradation when in contact with bodily fluids or aggressive drugs such as 5-Fu [6, 7]. Degradation can be reduced by applying protective coatings onto the internal and/or external surfaces of the catheters [8, 9]. Among the materials used for coating purposes, noble metals (silver and argentic

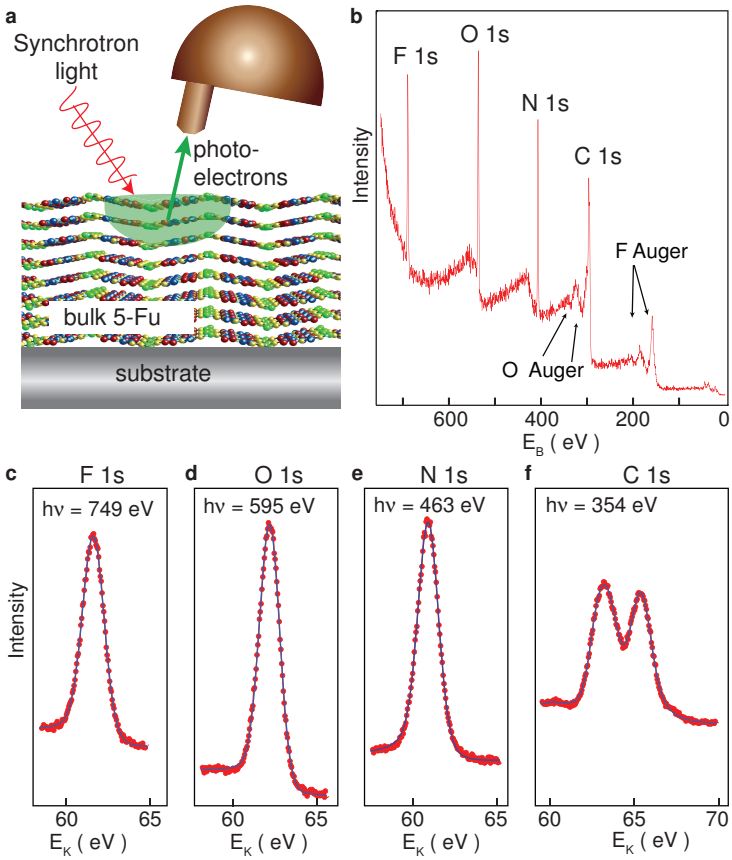

FIG. 1. **Photoemission spectroscopy of a bulk-like 5-Fu sample: a,** Schematic of the photoemission process and the depth sensitivity of the experiment. **b,** An overview measurement of the bulk-like 5-Fu sample (photon energy $h\nu$=800 eV, temperature -170 °C). **c-f,** Detail of the F1s, O1s, N1s and C1s regions respectively, measured with lower kinetic energy and higher resolution (≈100 meV). The raw experimental data (red) and a fit to the data (blue). Details of the fit and of the quantitative analysis are reported in the supplementary material.

alloys [10–13]) are particularly common because of their low reactivity and antimicrobial properties [14–17]. Despite the efforts made to improve the quality of the treatments of cancer and the life expectancy of the patients, investigation of a possible chemical reaction between coating materials and the chemotherapeutic drug itself is lacking (although some studies of the electronic interaction exist, see for example Ref. 18). In this work, we study the degradation of 5-Fu by silver surfaces, we report that HF is formed as a product, and we demonstrate graphene coatings to be an inert alternative.

Although X-ray photoemission spectroscopy (XPS) is a powerful technique for studying organic molecules (including uracil [19]), to the best of our knowledge no XPS studies of 5-Fu exist. Therefore, we first present our study of a 'bulk-like' 5-Fu layer. Since the depth sensitivity in an XPS experiment is limited by the mean-free-path of the photoemitted electrons (typically ≈1 nm), a 4 nm thick film of 5-Fu is sufficiently thick to be considered bulk-like. Indeed, our XPS study reveals that only the molecules, and not the underlying substrate, contribute to the signal (the XPS technique and depth sensitivity are represented schematically in Fig. 1a, and an overview XPS measurement in Fig. 1b). In our investigation of bulk-like films, we also measured the 1s core level spectra for nitrogen, fluorine, oxygen and carbon at low kinetic energy, and these results are summarized in Fig. 1c-f.

Quantitative analysis of the XPS data allows us to confirm the stoichiometry of the molecular film. 5-Fu is composed of C, F, N and O in a ratio $4 : 1 : 2 : 2$, and this is in good agreement with the experimentally determined abundance $4.6 : 1 : 2.2 : 1.8$ (measured relative to F, which is defined as unity). The multiple contributions to the C1s core level signal indicate that carbon is present in multiple bonding configurations with dissimilar binding energies. Furthermore, we carried out a similar XPS study on a bulk-like film prepared from powder (i.e. not thermally evaporated in vacuum) to show that 5-Fu is not damaged by evaporation (see supplementary material).

A thin film (≈0.7 nm) film of 5-Fu was also prepared on an Ag substrate. XPS measurements (Fig. 2a) reveal that a reaction takes place at body temperature (≈35 °C). Measurements were also performed at lower temperatures in order to reduce the thermal energy available (i.e. to facilitate observation of the intermediate steps of the reaction and their approximate energy budget).

Our study reveals that already at -170 °C the N1s core level undergoes a significant change from its bulk form, indicating a change in the N bonding configuration. A new

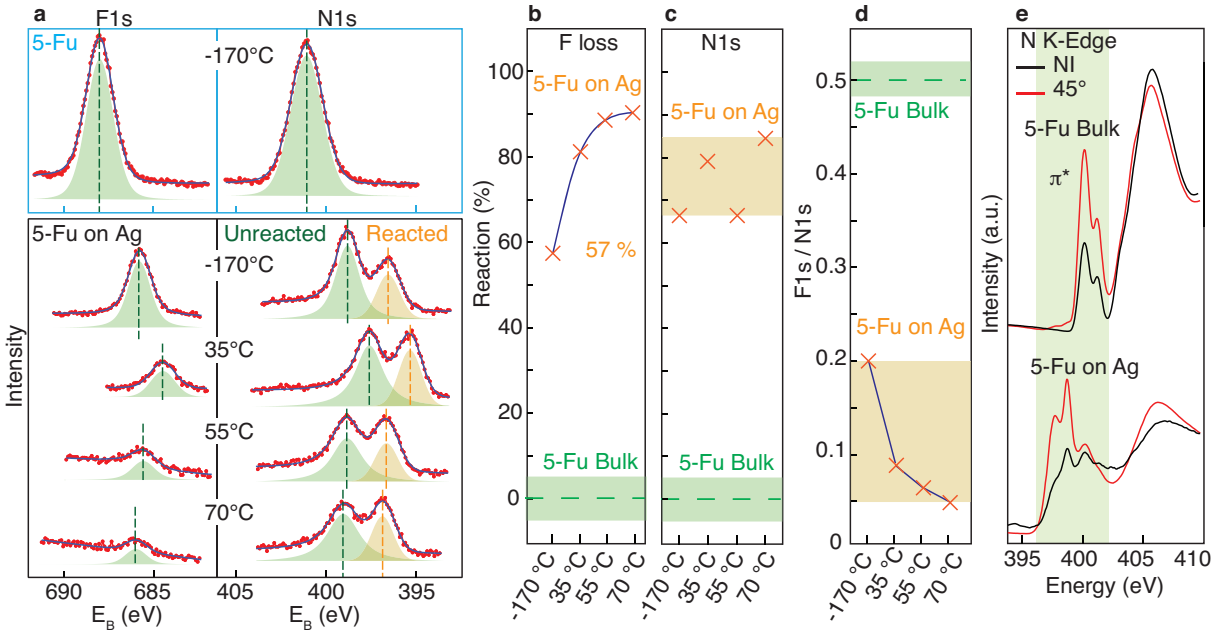

FIG. 2. **The reaction of 5-Fu with an Ag substrate: a,** XPS measurements of the N1s and F1s core levels of bulk 5-Fu (upper panel) and 5-Fu on Ag (lower panel). The green (orange) color indicates unreacted (reacted) chemical states. Raw data (red) and fits (blue) are shown. The reacted component of the N1s spectra appears at lower binding energy (≈2.2 eV with respect to the unreacted component). Both F1s and N1s show a shift (due to a charge transfer induced by doping) indicated by the dashed lines. The intensities of the core levels have been normalized to the synchrotron beam current and acquisition time. The photo-ionization cross section has been considered for the quantitative analysis (see supplementary material). **b,** The proportion of F lost from the surface. **c,** The proportion of 5-Fu molecules containing a reacted N atom. **d,** The F1s/N1s ratio as function of temperature. **e,** Nitrogen XAS measurements at two different incidence angles for 5-Fu on Ag revealing a change in the π-bonding as compared to a bulk-like sample.

'reacted' N1s core level component is observed at larger binding energy, shifted 2.2 eV from the unreacted component. We propose that the reaction involves breaking one of the N-H bonds with a subsequent H loss from the molecule. Assuming that only one N-atom per molecule is able to react, quantitative analysis of the N1s components indicates that ≈80% of the molecules are in the reacted form (Fig. 2c). The reaction is already favourable at the lowest temperature studied (-170 °C), and thus increasing the temperature is not seen to

play a significant role.

Analysis of the F1s peak also reveals that a reaction is taking place – seen as a relative reduction of the F1s intensity, indicating that fluorine is lost from the surface. The fluorine reduction shows a strong temperature dependence (Fig. 2b); at low temperature, the loss is ≈57% (relative to the bulk-like film), and as the temperature is increased to body temperature and above, the loss is almost complete (≈90%). The same behavior can also be observed by extracting the F1s/N1s intensity ratio (=0.5 for bulk 5-Fu) which is reduced to ≈0 as the temperature is increased (Fig. 2d).

Although the N1s and F1s peaks show signs of a reaction, the only modification to the O1s and C1s peaks (see supplementary material for details) is an energy shift which is similarly affects all of the thin film's core levels. We therefore conclude that the O and C-atoms are not involved in the reaction. The ubiquitous core level shift to lower binding energy (relative to the bulk film) is exhibited by all of the core levels, due to the *p*-type doping nature of the 5-Fu molecules and reaction fragments. The detail of the charge transfer between substrate and molecules is the subject of further study, however, the general principle that strongly *p*-type halogenated species cause a electronic re-alignment of the interface is not unusual [20]

Summarizing the XPS measurements, we observe that 5-Fu in contact with Ag gives rise to reactions which modify the bonding of one of the N-atoms in the 5-Fu molecule, and involves a massive F loss under vacuum conditions. We present a plausible reaction which is consistent with these observations 5-Fu $\rightarrow$ HF+$C_4H_2N_2O_2$. Where the a modification of an N-atom occurs, and is already favourable with minimal thermal energy (i.e. at low temperature), the loss of F requires a moderate energy budget - indicative of a reaction where the mobility of the atomic species on the silver surface plays a role. At body temperature both of these reactions are favourable and the vast majority of the molecules are seen to have reacted.

X-ray absorption spectroscopy (XAS) measurements of 5-Fu on Ag also support the notion of a change in the molecular π-bonding configuration of the molecule (Fig. 2e). Compared to the bulk-like sample, 5-Fu on Ag shows additional features at lower photon energies, in the energy range corresponding to a transition from the N1s core level to an unoccupied $\pi^\star$ orbital (indicated by the green area in Fig. 2e). This result suggests that the π-bonding of an N-atom has been significantly modified, but that a delocalised π state still remains. This

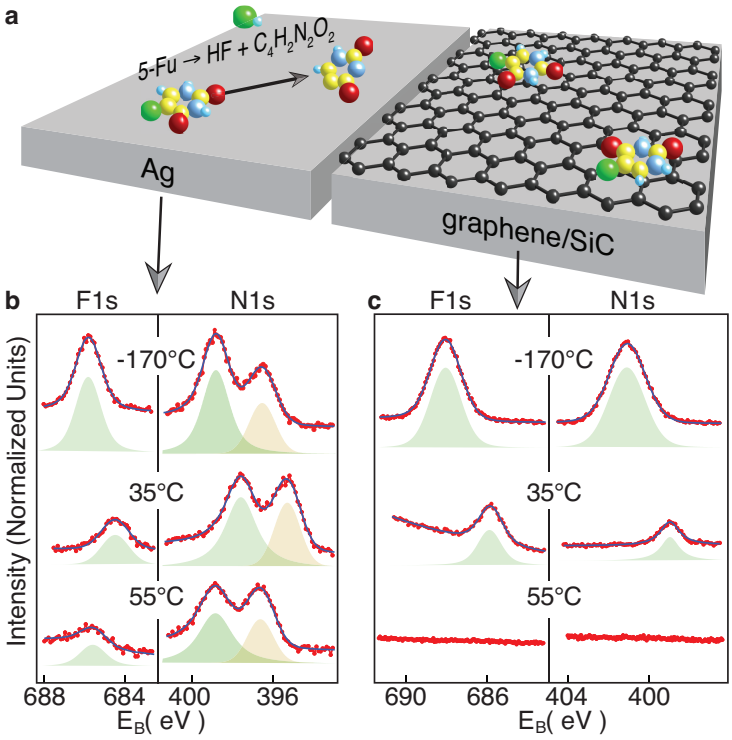

FIG. 3. **The interaction of 5-Fu with graphene and silver: a,** Schematic represention of 5-Fu in contact with Ag and graphene surfaces. **b,** Temperature dependent F1s and N1s XPS measurements of 5-Fu on Ag. **c,** The same temperature dependence for 5-Fu on graphene. No reaction is seen, and at T=55 °C the molecules have been completely desorbed, emphasising the weak interaction between 5-Fu and graphene.

view is consistent with the XPS inference of a silver-mediated reaction involving the breaking of an N-H bond. For both the bulk film and 5-Fu on Ag, the $\pi^\star$ absorption features are reduced at normal incidence (NI) relative to the measurement at 45° incidence, indicating that the molecules have a preference to lie flat on the substrate. For the bulk film, the molecular orientation can be rationalised using the bulk crystal structure. For the thin film 5-Fu on Ag, the molecular orientation is consistent with the orientation expected for the reacted species, and with STM observations (see supplementary material for the bulk crystal structure and STM measurements).

The reaction observed on the Ag surface is not seen on graphene. Graphene is chosen because we expect it to be chemically inert, and because it already attracts attention as the ultimately thin protective coating [21–23]. However, its potential as a nanoscale coating

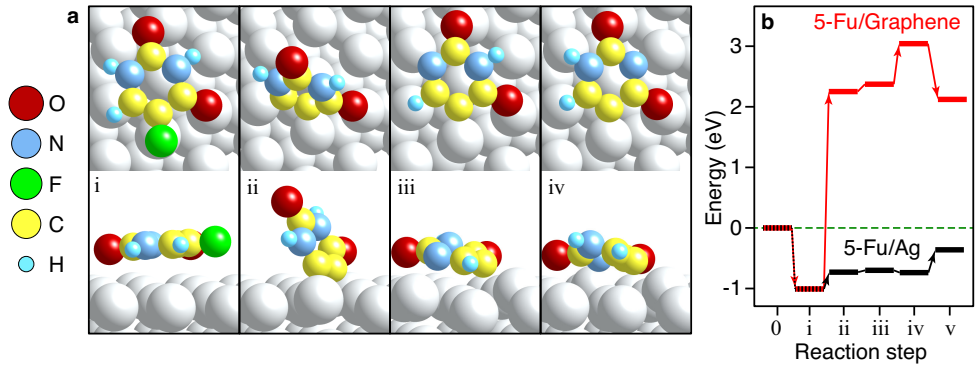

FIG. 4. **DFT calculated reaction pathway for 5-Fu on Ag and DFT optimised reaction products: a,** Top and side views of four of the reaction steps are shown (labelled i-iv). Note that after step i, H and F remain bound to the surface, but are not shown in the figure. **b,** The energy diagram for this reaction pathway for both 5-Fu on Ag and 5-Fu on graphene. The initial energy is zero by definition, and the absorption energy of 5-Fu on the two surfaces (step i) is very similar. However, the energy of the decomposition (step ii) is dramatically different.

material in chemotherapeutic drug delivery systems appears to have been entirely overlooked [24]. Graphene is a bio-compatible material [25, 26] with low toxicity. The accidental release of small quantities of a graphene coating into a patient is less concerning than a similar release of alternative coating materials.

A thin film (≈0.7 nm) of 5-Fu on graphene was prepared by thermal evaporation, following the same procedure as above. i.e., the only difference with the experiment of 5-Fu on Ag is that a graphene substrate is used in place of Ag. Temperature dependent XPS data have also been acquired (Fig. 3c) and compared with that from 5-Fu on Ag (Fig. 3b). Contrary to 5-Fu on Ag, the chemotherapy molecules on graphene do not react at any temperature; instead they are simply desorbed at moderate temperatures. This observation supports the idea of a weak interaction between graphene and 5-Fu since already at ≈55 °C the intact 5-Fu molecules have left the surface and no N or F can be detected by XPS.

DFT structural optimisation calculations have also been performed with results which support our experimental findings. Fig. 4 shows four of the steps of the suggested 5-Fu+Ag reaction pathway. The first step (i) involves the absorption of the molecule onto the Ag(111) surface; it is seen to be weakly physisorbed, and the total energy is lowered by ≈1 eV. In step ii, the C-F bond and a C-H bond are broken, resulting in a small increase in the total

energy which is feasible even at low temperature. H and F are liberated from the molecule and stay bound to the Ag surface. In steps iii and iv, reaction product is stabilised by a redistribution of both chemical bonding and charge transfer and the remaining H-atoms of molecule fragment rearrange, with negligible change in the energy. Finally, in step v (not shown), H and F recombine and an HF molecule is desorbed from the surface. This last step requires a moderate input of energy, which is consistent with the measured temperature dependence.

To summarize the DFT calculation reaction pathway, the molecules react at low temperature and the bonding in the vicinity of one N-atom is modified with the macrocycle remaining intact. Although H and F are already 'lost' from the 5-Fu molecule, the HF recombination and liberation from the surface cannot occur without a moderate amount of thermal energy. In agreement with the observation of HF in our residual gas analysis, these calculations support that HF, rather than F_2, is the favoured product (see the supplementary material for details of the residual gas analysis and the calculated energetics of the F_2 formation).

An identical reaction pathway has been calculated for 5-Fu on graphene (see Fig. 4b). Contrary to the situation for Ag, step ii requires a large energy input ($\approx$3 eV), which is prohibitive. In fact, the required energy is much larger than the absorption energy (step i), hence as the thermal energy is increased, the intact molecule would desorb well before it has the possibility to decompose. Unlike Ag, graphene is not able to stabilise the reaction by a redistribution of chemical bonds and charge transfer (i.e. compare the energy of steps ii to iv for the two surfaces).

The DFT calculations also support that the molecules have a tendency to lie flat on both the Ag and graphene substrate (which is unsurprising since molecules with conjugated π-systems typically show this tendency [27, 28]). The calculated orientation is consistent with the orientation observed with XAS and STM. Finally, the DFT calculation gives access to the binding energy of the reaction species; the two inequivalent N-atoms in the reacted molecular fragments have N1s components separated by 1.7 eV (compared to a calculated N1s separation of 0.4 eV for unreacted 5-Fu), this is in good agreement with the experimentally determined value of 2.2 eV.

At temperatures in excess of 70°C, the molecule fragments are observed to desorb from the Ag surface. Since the Ag surface plays a role in stabilising the reaction product, it is

unclear whether further reaction steps occur after desorption. The low energy barrier for re-distributing the molecular fragment's remaining H-atoms indicates that such a redistribution cannot is possible.

Using surface chemistry techniques in combination with DFT calculations, we observed that a reaction takes place for 5-Fu on silver which does not occur for 5-Fu on graphene. Our experiments have been performed on model surfaces in a well controlled ultrahigh vacuum environment ($P \leq 10^{-9}$ mbar). Although the experimental conditions necessarily differ from *in operando* drug delivery (most notably, the lack of ionic solution), it is of concern that an energetically favourable reaction exists in which 5-Fu is decomposed by Ag with HF as a product – especially when this reaction is readily avoided by choosing a more suitable coating material.

We conclude that silver and argentic alloys are not be a good choice for catheters delivering 5-Fu. Catheter degradation is a common problem, and our measurements indicate a likely cause; the catalytic degradation of 5-Fu by silver with HF as a product. We speculate that the presence of HF in the drug solution accounts, at least partially, for the prevalent degradation of catheters and their coatings. Such a reaction occurring in a real catheter would not only compromise the efficacy of the treatment, but also create concerns that Ag and HF are assimilated into the bloodstream of a patient [29, 30].

Since the potential effects of 5-Fu degradation are so significant, it is surprising that studies of the relevant catheter surface chemistry do not appear to have been carried out, and we believe that our study represents an important first step in exploiting established surface science methods in this field. Our study demonstrates that surface chemistry approaches are well suited to study the interaction of chemotherapeutic drugs on relevant surfaces.

Graphene has already been suggested as an external coating for bio-medical applications, and based on our finding, we propose to use graphene also for the internal surfaces. The fabrication of thin carbon-based coatings is technologically realistic [31–33]; graphene can even be grown directly on top of silver [34, 35], if desired, to maintain compliance with existing fabrication methods. We believe that graphene coatings will offer a vastly superior alternative to silver-based coatings, and can return a societal benefit within a short timescale.

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Nanotechnology for Microsystems, sponsored by the Research Council of Norway (contract no. 221860/F40). The calculation power is granted by The Norwegian Metacenter for Computational Science (NOTUR), project numbers: nn9229k and nn4504k.

Methods: The 'powder' sample was prepared by dissolving 5-Fu powder (>99%, Sigma-Aldrich, F6627-5G) in de-ionised water, followed by dripping the solution onto a tantalum sample plate and allowing it to dry under atmospheric conditions. After drying, a thick white powder layer was observed.

All other 5-Fu films were made by thermal evaporation under ultra-high vacuum (UHV) conditions. The same 5-Fu powder was placed in a tantalum crucible and heated in-vacuum until it evaporated. The substrate was held in front of the crucible and exposed to the molecular flux.

Prototype graphene samples were fabricated using standard CVD instrumentation in NTNU NanoLab. The high quality graphene sample was thermally grown on SiC with standard methods described in our previous work [36]. The Ag sample was a (111) single crystal which had been prepared in vacuum by cycles of sputtering and annealing.

Photoemission measurements were carried out at beamline D1011 at the MAX IV laboratory (Lund, Sweden). The thermally evaporated films were grown at the beamline and measured without exposure to air.

Samples were prepared for STM analysis by similar thermal evaporation in UHV.

Calculations were performed using Quantum Espresso [37]. We employed the generalized gradient approximation (GGA) method PBE functional [38] with Van der Waals correction [39] using an ultra soft pseudo-potential [40]. Satisfactory convergences were obtained with cutoffs of 70 Ry on the plane waves and 700 Ry on the electronic density. These conditions were checked to get a convergence of properties and lattice parameter of Ag bulk of 4.15 Å (experimental value 4.09 Å) [41] We used the Γ point for the k-point sampling of the Brillouin zone.

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